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		E	POHLMAN EDWARD C/IN
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L18	4	S	L12 AND PY=1994

L1 ANSWER 1 OF 2 USPATFULL
1998:33578 Introduction of HIV-protective genes into cells by particle-mediated gene transfer.
Nabel, Gary J., 3390 Andover Rd., Ann Arbor, MI, United States 48105
Woffendin, Clive, 3509 Burbank Dr., Ann Arbor, MI, United States 48105
Yang, Nin-Sun, 7802 Oxtrail Way, Verona, WI, United States 53593
Sheehy, Michael J. , 629 Piper Dr., Madison, WI, United States 53711
US 5733543 19980331
APPLICATION: US 1994-235277 19940429 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Foreign genes may be stably introduced into T cells, monocytes, macrophages, dendrites, and hematopoietic stem cells by particle-mediated gene transfer. Introduction of an HIV protective gene into the cells of a patient infected with HIV by particle-mediated gene transfer is effective for the treatment of HIV infection.

CLM What is claimed is:
1. A method for prolonging T cell survival in a HIV infected patient, comprising: (i) removing a plurality oft cells from a said patient; (ii) introducing, by particle mediated gene transfer, a gene encoding a product which inhibits HIV replication into said plurality of T cells; and (iii) reintroducing said plurality of T cells into said patient, wherein said gene encoding a product which inhibits HIV replication is Rev M10.

2. The method of claim 1, wherein said gene is under the operational control of a sequence of DNA such that the expression of said gene is stimulated by the expression of HIV.

3. The method of claim 1, wherein said gene is contained in a plasmid and is downstream from the TAR sequence such that expression of the gene is activated by Tat.

4. The method of claim 3, wherein said plasmid is pRSVtRevM10.

5. The method of claim 1, wherein said introducing by particle mediated gene transfer is carried out by introducing particles on which said gene is coated into said plurality of T cells, wherein said particles are made of a material selected from the group consisting of inert metals and inert plastics.

6. The method of claim 5, wherein said particles are made of a material selected from the group consisting of gold, silver, platinum, tungsten, polystyrene, polypropylene, and polycarbonate.

7. The method of claim 5, wherein said particles are gold particles.

8. The method of claim 5, wherein said particles have a diameter of 0.5 to 5 microns.

9. The method of claim 5, wherein said particles have a diameter of 1 to 3 microns.

10. The method of claim 5, wherein said gene is contained in a plasmid and said particles are gold particles, and said plasmid is coated on said particles in an amount of 3 to 30 micrograms of plasmid per milligram of particles.

11. The method of claim 10, wherein said particles are coated with an encapsulating agent before being coated with said plasmid.

12. The method of claim 11, wherein said encapsulating agent is polylysine.

13. The method of claim 1, wherein said gene is introduced into 10.sup.9 to 10.sup.13 T cells.

14. The method of claim 1, wherein said gene is introduced into 10.sup.10 to 10.sup.11 T cells.

15. The method of claim 1, wherein said introducing results in said gene being introduced into 1 to 10% of said plurality of T cells.

16. The method of claim 1, wherein steps (i), (ii), and (iii) are repeated a number of times sufficient to result in the introduction of said gene into 0.1 to 30% of said patient's T cells.

17. The method of claim 1, wherein steps (i), (ii), and (iii) are repeated a number of times sufficient to result in the introduction of such gene into 1 to 15% of said patient's T cells.

18. The method of claim 1, wherein said steps (i), (ii), and (iii) are carried out 1 to 10 times.

19. The method of claim 1, wherein said steps (i), (ii), and (iii) are carried out 2 to 5 times.

20. The method of claim 1, wherein said steps (i), (ii), and (iii) are repeated after 2 to 24 hrs.

L2 ANSWER 8 OF 9 USPATFULL
91:38416 Particle-mediated transformation of soybean plants and lines.
Christou, Paul, Madison, WI, United States
McCabe, Dennis, Middleton, WI, United States
Swain, William F., Madison, WI, United States
Barton, Kenneth A. , Middleton, WI, United States
Agracetus, Middleton, WI, United States (U.S. corporation)
US 5015580 19910514
APPLICATION: US 1988-193357 19880512 (7)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method and apparatus is disclosed for the genetic transformation of soybean plants and plant lines by particle mediated transformation. Foreign genes are introduced into regenerable soybean tissues by coating on carrier particles which are physically accelerated into plant tissues. The treated plant tissues are then recovered and regenerated into whole sexually mature plants. The progeny are recovered from seed set by these plants and a portion of these progeny will contain in their genome the foreign gene. The procedure may be used to create novel genetically engineered soybean plants and lines.

CLM What is claimed is:
1. A method of making a genetically transformed soybean plant comprising the steps of: preparing copies of a foreign gene including a coding region and flanking regulatory sequences effective to express the coding region in soybean cells; joining copies of the foreign gene to biologically inert carrier particles; placing an embryonic axis from a

soybean seed on a target surface; physically accelerating the particles carrying the foreign gene copies at the target surface in such a fashion that some particles lodge in the interior of at least some of the cells of the soybean embryonic acid; inducing shoot formation directly from the embryonic axis by hormone treatment without intermediate proliferation of tissue in callus culture; cultivating the shoot into a whole sexually mature soybean plant; and verifying the existence of the foreign gene in the tissues of the regenerated plant.

2. A method as claimed in claim 1 wherein the biologically inert particles are metallic.

3. A method as claimed in claim 2 wherein the metallic particles are gold spheres.

4. A method as claimed in claim 1 wherein the embryonic axis is from an excised zygotic embryo.

5. A method as claimed in claim 1 wherein the foreign gene is prepared as a plasmid hosted in a bacteria.

6. A method as claimed in claim 5 wherein the plasmid is pCMC1022 having ATCC accession number 67269.

7. A method as claimed in claim 5 wherein the plasmid is pCMC1100 having ATCC accession number 67641.

8. A method as claimed in claim 1 wherein the embryonic axis is placed on a target surface by plating such an excised tissue on a bed of an agar medium.

9. A method as claimed in claim 1 wherein the verifying the presence of the foreign gene is done by a hybridization assay for the presence of the foreign DNA itself.

10. A method as claimed in claim 1 wherein the verifying the presence of the foreign gene is done by an assay for the expression product of the foreign gene.

11. A method as claimed in claim 1 wherein the hormone treatment includes cultivation on a cytokinin containing medium to induce shoot formation.

12. A method as claimed in claim 1 wherein the step of cultivating the shoot into a whole plant includes the step of grafting the shoot onto a germinating soybean rootstock.

13. A method as claimed in claim 1 wherein the step of physically accelerating the particles carrying the foreign gene at the target surface includes placing the carrier particles on a planar carrier sheet, accelerating the carrier sheet with a shock wave, and stopping the carrier sheet while permitting the carrier particles to travel on toward the target surface.

14. A method as claimed in claim 13 wherein the carrier sheet is formed of aluminized mylar.

15. A method of making a genetically transformed line of soybean plants comprising the steps of: preparing copies of a foreign gene including a coding region and flanking regulatory sequences effective to express the coding region in soybean cells; joining copies of the foreign gene to

substantially biologically inert carrier particles; placing a meristematic soybean tissue comprising the embryonic axis from a soybean seed on a target surface; physically accelerating the particles carrying the foreign gene copies at the target in such a fashion that some particles lodge in the interior of at least some of the cells of the embryonic axis; inducing by hormone treatment shoot formation directly from the embryonic axis without intermediate callus cultivation of the tissue; cultivating the shoot into a whole sexually mature regenerated plant; obtaining self-pollinated seed from the sexually mature regenerated plant; growing up progeny plants from the seed; and verifying the existence of the foreign gene in the tissues of at least some of the progeny plants.

16. A method as claimed in claim 15 wherein the biologically inert particles are metallic.

17. A method as claimed in claim 15 wherein the metallic particles are gold.

18. A method as claimed in claim 15 wherein the meristematic soybean tissue is an excised zygotic embryo.

19. A method as claimed in claim 15 wherein the meristematic soybean tissue is placed on a target surface by plating such an excised tissue on a bed of an agar medium.

20. A method as claimed in claim 15 wherein the verifying the presence of the foreign gene is done by a hybridization assay for the presence of the foreign DNA itself.

21. A method as claimed in claim 15 wherein the verifying the presence of the foreign gene is done by an assay for the expression product of the foreign gene.

22. A method as claimed in claim 15 wherein the hormone treatment includes cultivation of a cytokinin containing medium to induce shoot formation.

23. A method as claimed in claim 15 wherein the step of cultivating the shoots into whole plants includes the step of grafting the shoots onto a germinating soybean rootstock.

24. A method of making a genetically transformed line of soybean plants comprising the steps of: preparing copies of a genetic construction including both a foreign gene and a marker gene, both genes including a coding region and flanking regulatory sequences effective to express the coding region of the gene in soybean cells; joining copies of the genetic construction to substantially biologically inert carrier particles; placing a plurality of embryonic axes from soybean seeds on a target surface; physically accelerating the particles carrying the foreign gene copies at the target in such a fashion that some particles lodge in the interior of at least some of the cells of the embryonic axes; inducing by hormone treatment shoot formation directly from the embryonic axes without intermediate callus cultivation of the tissue and without cell selection; screening the shoots for expression of the marker gene; cultivating the shoots expressing the marker gene into whole sexually mature regenerated plants; obtaining self-pollinated seed from the secularly mature regenerated plants; growing up progeny plants from the seeds; and verifying the existence of the genetic construction in the tissue of at least some of the progeny plants.

L4 ANSWER 97 OF 98 USPATFULL
92:46984 Apparatus for genetic transformation.
McCabe, Dennis E., Middleton, WI, United States
Martinell, Brian J., Madison, WI, United States
Glaser, Donald A., Berkeley, CA, United States
Agracetus, Inc., Middleton, WI, United States (U.S. corporation)
US 5120657 19920609
APPLICATION: US 1989-422921 **19891017** (7)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An apparatus is disclosed for the genetic transformation of organisms by accelerated ***particle*** ***mediated*** ***transformation*** . Foreign genes are introduced into cells by coating on carrier particles which are physically accelerated into the cells by positioning the carrier particles on a carrier sheet which is accelerated by a device which produces a shock wave. The treated cells are recovered, and a portion of them will contain in their genome the foreign gene. The procedure may be used to create genetically engineered organisms of many types.

L4 ANSWER 92 OF 98 USPATFULL
95:101121 Method for introducing a biological substance into a target.
Fitzpatrick-McElligott, Sandra G., Media, PA, United States
Lavin, John G., Swarthmore, PA, United States
Rivard, Germain F., Philadelphia, PA, United States
Subramoney, Shekhar, Hockessin, DE, United States
E. I. Du Pont de Nemours and Company, Wilmington, DE, United States (U.S. corporation)
US 5466587 19951114
APPLICATION: US 1994-315309 **19940929** (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for introducing a biological substance into a target which utilizes particles having a substantially pure carbonaceous surface to which is associated a biological substance wherein the particles are sufficiently small to penetrate the target without killing the target is described.

L4 ANSWER 91 OF 98 USPATFULL
95:105698 ***Particle*** - ***mediated*** ***transformation*** of mammalian unattached cells.
Yang, Ning-Sun, 7802 Ox Trail Way, Verona, WI, United States 53593
Swain, William F., 4922 Marathon Dr., Madison, WI, United States 53705
Burkholder, Joseph K., 917 Midland St., Madison, WI, United States 53715
Fuller, Deborah L., 6701 Park Edge Dr. Apt. D, Madison, WI, United States 53719
US 5470708 19951128
APPLICATION: US 1993-61430 **19930402** (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of genetically transforming mammalian unattached cells is disclosed. The method begins by preparing copies of a nucleic acid construct and coating these copies onto biologically inert carrier particles. Mammalian unattached cells are isolated in a liquid suspension. The cell suspension is placed on a target surface, wherein the liquid is spread to a thin film on the target surface. In an alternative embodiment of the present invention, the liquid is spread

onto a porous surface. The cells are bombarded with the construct-coated particles in such a fashion that some particles lodge in the interior of at least some of the cells. The existence and expression of the construct within the cell is verified.

L4 ANSWER 83 OF 98 USPATFULL
96:115820 Gas driven gene delivery instrument.
McCabe, Dennis E., Middleton, WI, United States
Agracetus, Inc., Middleton, WI, United States (U.S. corporation)
US 5584807 19961217
APPLICATION: US 1995-376319 **19950120** (8)
DOCUMENT TYPE: Utility.

AB A gas driven apparatus for accelerating particles coated with a genetic material into a target comprises a reservoir for releasably retaining a gas at a sufficiently high pressure to detach the particles from the surface of a sample cartridge and to carry the particles through the apparatus toward the target. When leaving the apparatus, the particles entrained in the gas stream pass through a substantially conical exit nozzle which causes the pattern of distribution of the particles to greatly expand. Methods for using the apparatus and for preparing the sample cartridges are also described.

L4 ANSWER 77 OF 98 USPATFULL
97:63909 Recombinant nucleic acids for inhibiting HIV gene expression.
Nabel, Gary J., Ann Arbor, MI, United States
Yang, Zhi-Yong, Ann Arbor, MI, United States
Liu, Jinsong, Randolph, NJ, United States
Woffendin, Clive, Ann Arbor, MI, United States
University of Michigan, Ann Arbor, MI, United States (U.S. corporation)
US 5650306 19970722
APPLICATION: US 1993-73836 **19930607** (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides recombinant nucleic acid molecules for enhanced expression of genes that inhibit HIV gene expression. Cells transfected with these recombinant nucleic acids exhibit prolonged cell life. This invention also provides methods of treating individuals infected with HIV by introducing into them the transfected cells of this invention.

L4 ANSWER 70 OF 98 USPATFULL
1998:33578 Introduction of HIV-protective genes into cells by ***particle*** - ***mediated*** ***gene*** ***transfer*** .
Nabel, Gary J., 3390 Andover Rd., Ann Arbor, MI, United States 48105
Woffendin, Clive, 3509 Burbank Dr., Ann Arbor, MI, United States 48105
Yang, Nin-Sun, 7802 Oxtrail Way, Verona, WI, United States 53593
Sheehy, Michael J., 629 Piper Dr., Madison, WI, United States 53711
US 5733543 19980331
APPLICATION: US 1994-235277 **19940429** (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Foreign genes may be stably introduced into T cells, monocytes, macrophages, dendrites, and hematopoietic stem cells by ***particle*** - ***mediated*** ***gene*** ***transfer*** . Introduction of an HIV protective gene into the cells of a patient infected with HIV by ***particle*** - ***mediated*** ***gene*** ***transfer*** is effective for the treatment of HIV infection.

L4 ANSWER 67 OF 98 USPATFULL
1998:82407 Method and apparatus for preparing sample cartridges for particle acceleration device.
McCabe, Dennis E., Middleton, WI, United States
Heinzen, Richard J., North Freedom, WI, United States
PowderJect Vaccines, Inc., Madison, WI, United States (U.S. corporation)
US 5780100 19980714
APPLICATION: US 1995-444173 19950518 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for depositing particles coated with biological substances onto the concave inner surface of a length of tubing includes the steps of preparing a uniform suspension of coated particles, introducing the particles into the tubing, placing the tubing into a generally horizontal position, removing the evaporable liquid after the particles have settled, and drying the particles. When dry, the tubing is cut into sample cartridges of appropriate length for use in a particle acceleration instrument.

An apparatus for performing the method is also disclosed.

AB Mammalian kringle 5 is disclosed as a compound for treating angiogenic diseases. Methods and compositions for inhibiting angiogenic diseases are also disclosed.

L4 ANSWER 29 OF 98 USPATFULL
2000:84490 Method for genetic transformation.
McCabe, Dennis E., Middleton, WI, United States
Martinell, Brian J., Madison, WI, United States
Glaser, Donald A., Berkeley, CA, United States
PowederJect Vaccines, Inc., Madison, WI, United States (U.S. corporation)
US 6084154 20000704
APPLICATION: US 1992-858818 **19920327** (7)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method and apparatus is disclosed for the genetic transformation of organisms by accelerated ***particle*** ***mediated*** ***transformation*** . Foreign genes are introduced into cells by coating on carrier particles which are physically accelerated into the cells. The treated cells are recovered, and a portion of them will contain in their genome the foreign gene. The procedure may be used to create genetically engineered organisms of many types.

L4 ANSWER 21 OF 98 USPATFULL
2000:117494 High efficiency genetic modification method.
McLaughlin-Taylor, Elizabeth, San Clemente, CA, United States
Kruger, Mark, Encinitas, CA, United States
Lundak, Cheryl, San Diego, CA, United States
Killion, Catherine, Long Beach, CA, United States
Chiron Corporation, Emeryville, CA, United States (U.S. corporation)
US 6114113 20000905
APPLICATION: US 1998-132541 19980811 (9)
PRIORITY: US 1997-55453 19970811 (60)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method is provided for producing a population of genetically modified T cells. In the method, an in vitro population of T cells is activated by contacting said population with a CD3 binding agent. Genetic modification is then carried out with the activated T cells by

contacting the same with a suitable gene transfer vector.

L4 ANSWER 13 OF 98 USPATFULL
2001:29541 Particle-mediated bombardment of DNA sequences into tissue to induce an immune response.
Johnston, Stephen A., Durham, NC, United States
Williams, R. Sanders, Durham, NC, United States
Sanford, John C., Geneva, NY, United States
McElligott, Sandra G., Rose Valley, PA, United States
Duke University, Durham, NC, United States (U.S. corporation)E.I. du Pont de Nemours & Company, Inc, Wilmington, DE, United States (U.S. corporation)Cornell Research Foundation, Inc., Ithaca, NY, United States (U.S. corporation)
US 6194389 B1 20010227
APPLICATION: US 1997-840224 19970411 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of transferring a gene to vertebrate cells is disclosed. The method comprises the steps of: (a) providing microprojectiles, the microprojectiles carrying polynucleic acid sequences, the sequences comprising, in the 5' to 3' direction, a regulatory sequence operable in the tissue cells and a gene positioned downstream of the regulatory sequence and under the transcriptional control thereof; and (b) accelerating the microprojectiles at the cells, with the microprojectiles contacting the cells at a speed sufficient to penetrate the cells and deposit the polynucleic acid sequences therein. Preferably, the target cells reside in situ in the animal subject when they are transformed. Preferred target cells are dermis or hypodermis cells, and preferred genes for insertion into the target cells are genes which code for proteins or peptides which produce a physiological response in the animal subject.

L4 ANSWER 12 OF 98 USPATFULL
2001:36806 Genetic induction of anti-viral immune response and genetic vaccine for filovirus.
Haynes, Joel R., Fort Collins, CO, United States
Schmaljohn, Connie S., Frederick, MD, United States
Fuller, Deborah L., Oregon, WI, United States
Schmaljohn, Alan, Frederick, MD, United States
Jahrling, Peter B., Middletown, MD, United States
PowerJect Vaccines Inc., Madison, WI, United States (U.S. corporation)
US 6200959 B1 20010313
APPLICATION: US 1996-760615 19961204 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An approach to genetic vaccine methodology is described. A genetic construction encoding antigenic determinants of a filovirus is transfected into cells of the vaccinated individuals using a particle acceleration protocol so as to express the viral antigens in healthy cells to produce an immune response to those antigens.

L7 ANSWER 41 OF 48 USPATFULL
97:63909 Recombinant nucleic acids for inhibiting HIV gene expression.
Nabel, Gary J., Ann Arbor, MI, United States
Yang, Zhi-Yong, Ann Arbor, MI, United States
Liu, Jinsong, Randolph, NJ, United States
Woffendin, Clive, Ann Arbor, MI, United States
University of Michigan, Ann Arbor, MI, United States (U.S. corporation)
US 5650306 19970722

APPLICATION: US 1993-73836 19930607 (8)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides recombinant nucleic acid molecules for enhanced expression of genes that inhibit HIV gene expression. Cells transfected with these recombinant nucleic acids exhibit prolonged cell life. This invention also provides methods of treating individuals infected with HIV by introducing into them the transfected cells of this invention.

L7 ANSWER 46 OF 48 USPATFULL
95:31803 Apparatus for genetic transformation.
McCabe, Dennis E., Middleton, WI, United States
Burkholder, Joseph K., Madison, WI, United States
Agracetus, Inc., Middleton, WI, United States (U.S. corporation)
US 5405779 19950411
APPLICATION: US 1993-45434 19930409 (8)
DOCUMENT TYPE: Utility.

AB An apparatus for the particle mediated genetic transformation of organisms in vivo has two parts, a support unit and a hand unit. The hand unit is of a convenient hand manipulable size so that it can be placed readily against the organism the cells of which are to be transformed. The hand unit is connected to the support unit by a flexible umbilical so that the hand unit can be placed where desired. The apparatus is particularly well adapted for the convenient transformation of somatic cells of whole animals or humans.

L7 ANSWER 48 OF 48 USPATFULL
91:38416 ***Particle*** - ***mediated*** ***transformation*** of soybean plants and lines.
Christou, Paul, Madison, WI, United States
McCabe, Dennis, Middleton, WI, United States
Swain, William F., Madison, WI, United States
Barton, Kenneth A., Middleton, WI, United States
Agracetus, Middleton, WI, United States (U.S. corporation)
US 5015580 19910514
APPLICATION: US 1988-193357 19880512 (7)
DOCUMENT TYPE: Utility.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method and apparatus is disclosed for the genetic transformation of soybean plants and plant lines by ***particle*** ***mediated*** ***transformation*** . Foreign genes are introduced into regenerable soybean tissues by coating on carrier particles which are physically accelerated into plant tissues. The treated plant tissues are then recovered and regenerated into whole sexually mature plants. The progeny are recovered from seed set by these plants and a portion of these progeny will contain in their genome the foreign gene. The procedure may be used to create novel genetically engineered soybean plants and lines.

L9 ANSWER 1 OF 38 MEDLINE
1999192998 Document Number: 99192998. PubMed ID: 10093038. Gene gun-mediated IL-12 gene therapy induces antitumor effects in the absence of toxicity: a direct comparison with systemic IL-12 protein therapy. Rakhmilevich A L; Timmins J G; Janssen K; Pohlmann E L; ***Sheehy M J*** ; Yang N S. (Cancer Gene Therapy, Auragen, Inc., Middleton, Wisconsin, USA.) JOURNAL OF IMMUNOTHERAPY, (1999 Mar) 22 (2) 135-44. Journal code: CUQ; 9706083. Pub. country: United States. Language: English.

AB Using three murine tumor models, we compared the antitumor efficacy and certain physiological effects of an in vivo interleukin-12 (IL-12) gene therapy protocol and a systemic IL-12 protein therapy protocol. An IL-12 cDNA gene construct was administered in situ into skin tissue via gene gun delivery, and recombinant IL-12 protein was administered subcutaneously at a dose of 1 microgram/mouse/treatment. Both treatment regimes induced a comparable level of regression of established intradermal MethA sarcomas. In B16 melanoma and P815 mastocytoma models, antitumor efficacy of IL-12 protein therapy appeared to be slightly higher than that of IL-12 gene therapy; however, the protein therapy protocol in this comparative study resulted in a high level of mortality of mice. It was also demonstrated that IL-12 gene therapy, in contrast to the IL-12 protein therapy, was not associated with weight loss, splenomegaly, increased Ly6 antigen expression in the spleen, or visible signs of toxicity, such as fur ruffling and lethargy. Moreover, serum levels of interferon-gamma (IFN-gamma) induced in response to IL-12 gene therapy were 300-1000 times lower than those induced by the systemic IL-12 protein administration. Together, these results suggest that gene gunmediated in vivo delivery of IL-12 cDNA may be considered as a safer alternative to IL-12 protein therapy for certain human cancers.

L9 ANSWER 2 OF 38 MEDLINE
1998209782 Document Number: 98209782. PubMed ID: 9550412. Immune responses induced by intramuscular or gene gun injection of protective deoxyribonucleic acid vaccines that express the circumsporozoite protein from Plasmodium berghei malaria parasites. Leitner W W; Seguin M C; Ballou W R; Seitz J P; Schultz A M; ***Sheehy M J*** ; Lyon J A. (Department of Immunology, Walter Reed Army Medical Institute of Research, Washington, DC 20307-5100, USA.) JOURNAL OF IMMUNOLOGY, (1997 Dec 15) 159 (12) 6112-9. Journal code: IFB; 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The circumsporozoite protein (CSP) is a target for effector Ab and cell mediated immunity against malaria parasites; DNA vaccination can induce both types of effector response. The immunogenicity and efficacy of two DNA plasmids expressing different amounts of Plasmodium berghei CSP were evaluated by immunizing BALB/c mice i.m. or epidermally and by varying the number of immunizations (one to three doses) and the interval between immunizations. Expanding the interval gave the strongest effect, increasing efficacy and antibody boosting, and, in the case of epidermal vaccination, promoting a switch in CSP-specific IgG isotypes from IgG1 to a balance with IgG2a. The strongest humoral immune response and the greatest level of protection were induced by vaccinating epidermally with high expresser plasmid, using a gene gun to administer three doses at 6-wk intervals. For this group, the mean, repeat-specific, prechallenge antibody titer among mice not infected after challenge was significantly higher than that in infected mice, but the mean prechallenge titers for antibody reactive with whole sporozoites were not significantly different. The interval-dependent induction of IgG2a antibodies by epidermal vaccination contradicts the widely held belief that antibody responses induced by this method are restricted to those that are Th2 dependent.

L9 ANSWER 3 OF 38 MEDLINE
1998091727 Document Number: 98091727. PubMed ID: 9429892. DNA cancer vaccines: a gene gun approach. Mahvi D M; ***Sheehy M J*** ; Yang N S. (Department of Surgery, University of Wisconsin School of Medicine, Madison, USA.) IMMUNOLOGY AND CELL BIOLOGY, (1997 Oct) 75 (5) 456-60. Ref: 34. Journal code: GH8; 8706300. ISSN: 0818-9641. Pub. country: Australia. Language: English.

AB A wide variety of approaches, all using gene transfer, have been tested experimentally as alternative means to vaccinate against cancer, either prophylactically or therapeutically. These include both ex vivo and in vivo gene transfer to tumour and/or non-tumour cells, using both viral and non-viral vectors. The transferred DNA has varied widely as well, including genomic or cDNA encoding tumour-associated or oncofoetal antigens, cytokines, histocompatibility molecules, and costimulatory molecules. Several of these approaches have been applied in human clinical trials. This review summarizes those approaches, then compares and evaluates various methods using cytokine DNA in conjunction with autologous tumour cells, with particular emphasis on particle-mediated gene transfer via a gene gun. Finally, prospects and needs for further development are discussed.

L9 ANSWER 4 OF 38 MEDLINE
96348748 Document Number: 96348748. PubMed ID: 8725884. Dual expression of human leukocyte antigen molecules and the B7-1 costimulatory molecule (CD80) on human melanoma cells after particle-mediated gene transfer. Albertini M R; Emler C A; Schell K; Tans K J; King D M; ***Sheehy M J*** . (University of Wisconsin Comprehensive Cancer Center, Madison, USA.) CANCER GENE THERAPY, (1996 May-Jun) 3 (3) 192-201. Journal code: CE3; 9432230. ISSN: 0929-1903. Pub. country: United States. Language: English.

AB The aim of this study was to determine if human melanoma cells could be molecularly modified by particle-mediated gene transfer with a "gene gun", using genes for interferon-gamma (IFN-gamma), the B7-1 costimulatory molecule (CD80), and human leukocyte antigen (HLA)-A2, to augment expression of both HLA molecules and B7-1. Established and early passage melanoma cells transfected with human IFN-gamma complementary DNA (cDNA) produced IFN-gamma (50-5,000 pg/mL). The biological effect of this IFN-gamma transgene included an upregulation, or de novo appearance, of HLA expression. These melanoma cells had no detectable baseline surface expression of the B7-1 costimulatory molecule, but 8% to 31% of these cells became B7-1 positive with no selection procedure after gene transfer with human B7-1 cDNA. After combination gene transfer with cDNAs for both IFN-gamma and B7-1, 9% to 33% of these cells expressed both HLA-DR and B7-1. In combination gene transfer experiments with cDNAs for both HLA-A2 and B7-1, dual expression of HLA-A2 and B7-1 was achieved in 10% to 17% of the melanoma cells. Thus, the molecular modification of human melanoma cells to increase expression of both HLA and B7-1 can be achieved by particle-mediated gene delivery and presents a promising strategy to stimulate antimelanoma T-cell immunity. Key words: Melanoma; T cells; B7-1 costimulatory molecule (CD80); major histocompatibility complex.

L11 ANSWER 22 OF 42 MEDLINE
1998416008 Document Number: 98416008. PubMed ID: 9744759. Transient transfection of primary T helper cells by ***particle*** - ***mediated*** ***gene*** ***transfer*** . Huang H; Pannetier C; Hu-Li J; Paul W E. (Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-1892, USA.) JOURNAL OF IMMUNOLOGICAL METHODS, (1998 Jun 1) 215 (1-2) 173-7. Journal code: IFE; 1305440. ISSN: 0022-1759. Pub. country:

Netherlands. Language: English.

AB The study of the molecular basis of normal CD4+ T cell function, such as the control of commitment to the TH1 or TH2 phenotypes has been difficult due to the resistance of these cells to transfection by conventional methods. We used antibodies specific to T cell surface molecules to immobilize these cells and optimized conditions for transiently transfecting them by means of ***particle*** - ***mediated*** ***gene*** ***transfer*** . Using this technique, a construct encompassing - 577 to +1 of the IL-4 promoter allowed transcription of a luciferase reporter gene in recently-differentiated TH2 cells stimulated by anti-CD3, consistent with regulation of endogenous IL-4 gene expression.

L11 ANSWER 26 OF 42 MEDLINE
1998020870 Document Number: 98020870. PubMed ID: 9382772. Manipulation of immune responses via particle-mediated polynucleotide vaccines. Swain W F; Macklin M D; Neumann G; McCabe D E; Drape R; Fuller J T; Widera G; McGregor M; Callan R J; Hinshaw V. (Auragen Inc., University Green, Middleton, WI 53562, USA.) BEHRING INSTITUTE MITTEILUNGEN, (1997 Feb) (98) 73-8. Ref: 23. Journal code: 9KI; 0367532. ISSN: 0301-0457. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Polynucleotide vaccines are a new approach to immunization that promises qualitative advances in vaccine technology. These vaccines mimic infection in that they result in expression of pathogen gene products in situ, which can elicit both cell-mediated immune responses and humoral responses. This approach has been applied primarily to vaccines against viral diseases, but may be significant for vaccines directed toward bacterial pathogens. Auragen has developed a generally applicable gene transfer technology and, for vaccine applications, has focused on ***particle*** - ***mediated*** ***gene*** ***transfer*** to epidermis. Results demonstrate that Accell polynucleotide vaccines induce immune responses toward human immunodefficiency virus (HIV) antigens, influenza A virus antigens, and hepatitis B virus (HBV) antigens in rodent,s swine and primates. Cellular immune responses toward these antigens have been demonstrated in rodents. In a swine influenza a challenge model Accell vaccination provides protection equivalent to that of a commercial killed-whole-virus vaccine. Vaccination of mice by this method toward a Chlamydia pneumoniae major outer-membrane protein elicits a species-specific antibody response.

L11 ANSWER 29 OF 42 MEDLINE
97103542 Document Number: 97103542. PubMed ID: 8947913. Developing ***particle*** - ***mediated*** ***gene*** - ***transfer*** technology for research into gene therapy of cancer. Yang N S; Sun W H; McCabe D. (Cancer Gene Therapy, Auragen Inc., Middleton, WI 53562, USA.. nsyang@agracetus.com) . MOLECULAR MEDICINE TODAY, (1996 Nov) 2 (11) 476-81. Ref: 30. Journal code: CMK; 9508560. ISSN: 1357-4310. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Gene therapy aims to (1) introduce specific genes into a host to replace defective ones (replacement therapy); (2) suppress expression of certain undesirable genes (antisense therapy); or (3) provide additional biological activities (supplement therapy). Naked DNA and viral or non-viral vectors containing candidate genes for human gene therapy are being actively pursued by researchers in molecular medicine. New gene transfer technologies are rapidly developing and some have proved to be powerful tools for medical research. This review discusses the development and application of ***particle*** - ***mediated*** ***gene*** ***transfer*** technology in experimental systems and its potential

clinical utilities.

L15 ANSWER 1 OF 1 MEDLINE
94089656 Document Number: 94089656. PubMed ID: 8265577. DNA vaccines: protective immunizations by parenteral, mucosal, and ***gene*** - ***gun*** inoculations. Fynan E F; Webster R G; Fuller D H; Haynes J R; Santoro J C; Robinson H L. (Department of Pathology, University of Massachusetts Medical School, Worcester 01655.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, ***(1993*** *** Dec 15)*** 90 (24) 11478-82. Journal code: PV3; 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Plasmid DNAs expressing influenza virus hemagglutinin glycoproteins have been tested for their ability to raise protective immunity against lethal influenza challenges of the same subtype. In trials using two inoculations of from 50 to 300 micrograms of purified DNA in saline, 67-95% of test mice and 25-63% of test chickens have been protected against a lethal influenza challenge. Parenteral routes of inoculation that achieved good protection included intramuscular and intravenous injections. Successful mucosal routes of vaccination included DNA drops administered to the nares or trachea. By far the most efficient DNA immunizations were achieved by using a ***gene*** ***gun*** to deliver DNA-coated gold beads to the epidermis. In mice, 95% protection was achieved by two immunizations with beads loaded with as little as 0.4 micrograms of DNA. The breadth of routes supporting successful DNA immunizations, coupled with the very small amounts of DNA required for ***gene*** - ***gun*** immunizations, highlight the potential of this remarkably simple technique for the development of subunit vaccines.

L18 ANSWER 3 OF 4 MEDLINE
95124254 Document Number: 95124254. PubMed ID: 7823871. ***Gene*** ***gun*** transfection of animal cells and genetic immunization. Johnston S A; Tang D C. (Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas 75235.) METHODS IN CELL BIOLOGY, ***(1994)*** 43 Pt A 353-65. Ref: 27. Journal code: MV4; 0373334. ISSN: 0091-679X. Pub. country: United States. Language: English.

AB ***Gene*** ***gun*** technology at this point has the most utility in animal protein expression as a back-up technology. In other words, when other conventional systems fail, it will generally work. Most notable is its usefulness for hard-to-transfect cells or in some particular in situ applications. Improvements in the gun itself and in the microprojectiles present the potential for this technology to expand in utility. The one area in which it now appears to be the method of choice is genetic immunization.

L18 ANSWER 1 OF 4 MEDLINE
95194703 Document Number: 95194703. PubMed ID: 7888198. A qualitative progression in HIV type 1 glycoprotein 120-specific cytotoxic cellular and humoral immune responses in mice receiving a DNA-based glycoprotein 120 vaccine. Fuller D H; Haynes J R. (Agracetus, Inc., Middleton, Wisconsin 53562.) AIDS RESEARCH AND HUMAN RETROVIRUSES, ***(1994 Nov)*** 10 (11) 1433-41. Journal code: ART; 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB The potential for eliciting humoral and cytotoxic T lymphocyte (CTL) responses to HIV-1 gp120 by ***gene*** ***gun*** -based DNA immunization in mice was examined. We speculated that the induction of de novo antigen production in the epidermis of BALB/c mice following particle bombardment-based gene delivery would result in both MHC class I- and class II-mediated antigen presentation for the elicitation of CTL and

antibody responses, respectively. Following epidermal delivery of microgram quantities of an expression plasmid, gp120 production resulted in the appearance of MHC class I-restricted, CD8+ CTL responses. gp120-specific CTL responses peaked following a booster immunization, then declined with the appearance of gp120-specific IgG responses when additional booster immunizations were administered. This qualitative progression in the nature of gp120-specific immune responses with subsequent immunizations was paralleled by a simultaneous shift in the interferon-gamma and interleukin 4 release profiles following antigen stimulation of splenocytes in vitro. The simultaneous shifts in immune responses and cytokine release profiles indicate that the progression of antigen-specific CTL and IgG responses in gp120 DNA-immunized mice may be mediated through changes in the in vivo production of cytokines, such as those associated with the Th1 and Th2 subsets of CD4+ cells.

L18 ANSWER 2 OF 4 MEDLINE
95185103 Document Number: 95185103. PubMed ID: 7879412. Protection of ferrets against influenza challenge with a DNA vaccine to the haemagglutinin. Webster R G; Fynan E F; Santoro J C; Robinson H. (Department of Virology and Molecular Biology, St Jude Children's Research Hospital, Memphis TN 38101-0318.) VACCINE, ***(1994 Dec)*** 12 (16) 1495-8. Journal code: X60; 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Immunization of ferrets with a plasmid DNA expressing influenza virus haemagglutinin (pCMV/H1 DNA) provided complete protection from challenge with the homologous A/PR/8/34 (H1N1) influenza virus. Delivery of DNA-coated gold beads by ***gene*** ***gun*** to the epidermis was much more efficient than intramuscular delivery of DNA in aqueous solution. The antibody response induced by DNA delivered by ***gene*** ***gun*** was more cross-reactive than DNA delivered in aqueous solution or after natural infection. This novel approach to vaccination against influenza may afford broader protection against antigenic drift than that provided by natural infection.